REMARKS

Claims 1-18, 20-39, and 51 constitute the pending claims in the present application. Applicants cancel, without prejudice, claims 38 and 39. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note with appreciation that the corrected drawings filed on August 21, 2003 have been approved.

2. Claims 12-18, 22, 24-25, 27, 29, 31, 33, 35, 37, 39 and 51 are objected to for being in improper form because a multiply dependent claim must refer to claims in the alternative and because a multiply dependent claim cannot depend from another multiply dependent claim. Applicants' amendments to the claims are believed to obviate the objection. Applicants' amendments are procedural in nature and do not alter the substance or scope of the amended claims. Reconsideration and withdrawal of this objection are requested.

3. Claim 28 is rejected under 35 U.S.C. 101 because the claimed is allegedly directed to non-statutory subject matter. Applicants traverse this rejection.

The Examiner alleges that claim 28 is directed to non-statutory subject matter. The Examiner appears to allege that claims directed to human cells constitute non-statutory subject matter *per se*. However, the Examiner's position is simply not supported by the position of the patent office in prosecuting other claims directed to human biological materials.

The prohibition against claims directed to human materials is a prohibition against claims that cover materials as they endogenously exist inside the human body. This position seems to make some sense in that we can't have every walking human being infringing presumptively valid US patents. However, such is not the case with claim 28. Claim 28 explicitly states that the human cells are ***isolated*** cells. Furthermore, the cells of claim 28 are isolated cells that have been manipulated to express the constructs of the present invention. Thus, given that the cells are both isolated and are manipulated to express exogenously supplied DNA, the human cells of claim 28 are not cells that exist in all of us, and claims directed to these cells do not constitute non-statutory subject matter.

In further support of Applicants' position, Applicants direct the Examiner's attention to the host of issued US patents containing claims directed to isolated human stem cells (see, e.g., US Patent No. 5,486,359, US Patent No. 5,591,625, US Patent No. 6,200,806, and US Patent No. 5,843,780). These recently issued US patents contain claims directed to isolated human cells – including both genetically modified cells and un-modified cells. The existence of these, and other, issued US patents containing claims directed to isolated human cells supports Applicants' position that there is no statutory prohibition against claims directed to such subject matter. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

4. Claims 26, 28, 30, 32, 34, and 38 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one of skill in the art to make or use the invention. Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

Applicants continue to be puzzled by this rejection which seems entirely based on whether Applicants have enabled one of skill in the art to make and use transgenic animals. The claims are directed to methods of expressing the subject constructs in various cells. Such methods have a variety of uses that are (a) clearly contemplated by the specification and (b) of utility independently of the making of transgenic animals.

Applicants direct the Examiner's attention to the following exemplary passages from the specification that demonstrate the variety of uses for cells expressing the subject constructs, as well as methods for expressing the subject constructs in cells (see, e.g., page 2, lines 4-10; page 3, line 31-page 4, line 7; page 4, line 27-page 5, line 3). Furthermore, Applicants have not merely described the subject methods, Applicants have provided working examples that demonstrate methods of expressing the constructs of the present invention in cells (see, Examples 4, 5, 8, etc.). Applicants' working examples demonstrate that the subject constructs can be expressed in cells, and further that the genetically engineered cells express functional proteins that are regulatable.

Applicants contend that the specification provides extensive guidance and working examples to enable one of skill in the art to practice the claimed invention. Applicants maintain all of the arguments of record regarding the well developed literature in the art concerning transgenic animals, however, Applicants further contend that regardless of the Examiner's view

on the making of transgenic animals, maintenance of this rejection based solely on such arguments is inconsistent with MPEP 2164. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." MPEP 2164.01(b); *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). Applicants contend that disclosure of working examples representative of subject matter within the scope of the pending claims clearly satisfies the requirements under 35 U.S.C. 112, first paragraph. Maintenance of his rejection not only deprives Applicants of reasonable patent protection based on the disclosure; maintenance of this rejection actually deprives Applicants of protection for the very working examples explicitly disclosed in the specification. Clearly, such a result is inconsistent with the MPEP, case law, and the purpose of the patent system.

In light of Applicants disclosure which bears a reasonable correlation to the scope of the pending claims, and in light of the well developed art in the making and using of genetically modified cells and organisms, Applicants contend that the pending claims are enabled throughout their scope. Reconsideration and withdrawal of this rejection are respectfully requested.

5. Claims 2-4, 20, 21, 23, 26, 28, 30, 32, 35, 36, and 38 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims and in light of the amendments to the specification.

The Examiner has cited MPEP 608.01(p) and alleges that this portion of the MPEP states that essential subject matter cannot be incorporated by reference from a non-patent reference. The Examiner further alleges that Applicants cannot amend the specification to include material from the cited reference without violating the prohibition against new matter. Applicants respectfully assert that the Examiner is simply incorrect.

Applicants' position is supported by extensive case law on the topic of incorporation by reference. Applicants note that the purpose of the rules governing incorporation by reference is to balance conservation of words and space by not requiring Applicants to recite verbatim subject matter that has already been eloquently stated in other documents with the need to properly inform the public regarding essential elements of an invention. Thus, even if it results

in economies of words and space, incorporation by reference may be improper if the referenced document is difficult to obtain. The need to balance these interests led to the idea that US patents and patent applications, which are publicly available and easily obtainable by members of the public, can be incorporated simply by reference to patent or application number. However, this does not mean that other non-patent references **cannot** be incorporated by reference. All that this means is that the patent office can, at its discretion, require Applicants to amend their specifications to expressly include essential subject matter disclosed in the cited reference. This interpretation of MPEP 608 is supported by MPEP 608(p)(I)(A)(2). "The filing date of any application wherein essential material is improperly incorporated by reference to a foreign application or patent **or to a publication** will not be affected because of the reference. In such a case, the applicant will be required to amend the specification to include the material incorporated by reference." (emphasis added).

Applicants' interpretation of MPEP 608(p) is further supported by recent case law. Applicants respectfully direct the Examiner's attention to *Telemac Cellular v. Topp Telecom*, 247 F.3d 1316, 1329, 58 U.S.P.Q.2d 1545 (Fed. Cir. 2001), which states, "[w]hen a document is 'incorporated by reference' into a host document, such as a patent, the referenced document becomes effectively part of the host document as if it were explicitly contained therein. *Advanced Display Sys. v. Kent State,* 212 F.3d 1272, 1282, 54 USPQ2d 1673, 1679 (Fed. Cir. 2000)." Of particular note is that *the entire document* is considered to be incorporated – not merely a portion. Other cases, should the Examiner choose to review them, reach a similar result. *Rolls Royce v. United States*, 339 F.2d 654, 168 Ct.Cl. 367 (Fed. Cir. 1964); *Technograph Printed Circuits v. Bendix Aviation*, D.C., 218 F.Supp. 1, 31, aff'd 327 F.2d 497 (4 Cir., 1964); *B. F. Goodrich v. U.S. Rubber*, D.C., 147 F.Supp. 40, 58, [FN11] aff'd 244 F.2d 468 (4 Cir., 1957).

Indeed, courts of appeals feel strongly about this issue: "Filing cabinets abhor redundancy. Warehouses covet their space. The overcrowded conditions of offices in this city are in direct ratio to the space needed for storing of documents. The Patent Office was conceived by a document and has been prolific in that regard from its inception. These considerations warrant an economizing of words so as to alleviate these serious conditions. We do not feel that this economy will be at the expense of clarity and thereby frustrate the effectiveness of the statute." *General Elec. Co. v. Brenner*, 407 F.2d 1258, 1263 (D.C. Cir. 1968).

Applicants contend that, in light of both the MPEP and the court, the claims satisfy all of the requirements of 35 U.S.C. 112, second paragraph, by referring to subject matter properly incorporated by reference into the application. Nevertheless, to expedite prosecution, Applicants have amended the specification and provided a substitute sequence listing to expressly incorporate essential subject matter disclosed in the two Guerini publications and the GenBank accession numbers. These references disclose the nucleic acid and amino acid sequences of calcineurin A and calcineurin B, and such sequences have now been explicitly recited in the present specification. Applicants contend that the amendments to the specification are fully supported by these references and do not constitute new matter. Furthermore, Applicants point out that, contrary to the Examiner's assertion, the Guerini references themselves refer to the amino acid sequences of calcineurin A and calcineurin B by amino acid number with reference to the N-terminus. Thus, use of a similar numbering system, commonly used in the art, with reference to the amino acid sequences of calcineurin A and calcineurin B fully complies with the requirements of 35 U.S.C. 112, second paragraph. Accordingly, in light of Applicants' amendments to the specification and to the claims, reconsideration and withdrawal of this rejection is respectfully requested.

Applicants point out for the record, however, that the entirety of these references is incorporated by reference into the disclosure. Applicants willingness to expressly incorporate subject matter requested by the Examiner in no way indicates that other subject matter that Applicants have not expressly incorporated into the specification has been surrendered. As outlined in detail above, such an interpretation would be completely contrary to the purpose of incorporation by reference and furthermore would be contrary to the recent holding of the courts.

6. Claims 1-2, 4, 11, 20-21, 26, 28, 34, and 36 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Guerini et al., PNAS, 1989, 86: 9183-9187 ("Guerini/PNAS"). Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

In making this rejection, the Examiner assumes that the term "portion" refers to a single amino acid residue, and thus the pending claims are anticipated by the cited reference. This assumption is important because if the term "portion" refers to larger fragments, the pending

claims are not anticipated by the cited reference which provides neither guidance nor motivation to make constructs comprising calcineurin A and B.

The meaning of the word "portion" must not be construed in a vacuum. Rather, the word's meaning must be interpreted in light of the specification and in light of the claim in which the word is used. Applicants contend that, in light of the specification and the context on which the term is used, the Examiner's interpretation of "portion" to mean a single amino acid residue is incorrect.

The specification discusses in detail exemplary CAB domains (pages 26-29). Although the specification discusses a variety of constructs comprising various "portions" of calcineurin A and B, the distinctive feature of each is that the portion of calcineurin A and B is sufficient to impart a useful functional property. For example, a portion of calcineurin A sufficient for calmodulin binding or autoregulatory activity, or a portion of calcineurin A or B sufficient for dimerization. Applicants contend that the term "portion" as used in the specification is refer to fragment greater than one amino acid residue. In other words, the term portion must mean a fragment sufficient to impart a functional property of calcineurin A or B.

The term portion must also be interpreted in light of its context in the claims. "Portion" describes calcineurin A or B - the claims are directed to constructs which contain a portion of calcineurin A or B. In the context of a recombinantly made nucleic acid construct, if the term portion means a single amino acid residue, how could one possibly determine if that single amino acid residue is a single residue of calcineurin A or B? If I give you a serine residue, and nothing else, could you tell me that this is a serine residue from calcineurin A? Calcineurin B? Insulin? FGF-1? Clearly, the answer is no. In the context of these claims, the term portion only has meaning if it is sufficient so that one can determine that the portion corresponds to a portion of calcineurin A or B. The Examiner's interpretation of "portion" leaves us wondering if the single amino acid residue (the "portion") corresponds to calcineurin A or B, or to some other unrelated protein.

Applicants contend that the rejection of the claims under 35 U.S.C. 102(b) is based entirely on the Examiner's interpretation of the term portion to include a single amino acid residue. As discussed in detail above, this interpretation is erroneous in light of Applicants' use of the term in the specification and in light of the use of the term in the context of the claim in which it appears. Accordingly, Applicants contend that the relevance of the cited reference must

instead be evaluated in light of an interpretation of portion to mean greater than a single amino acid residue. The cited reference neither teaches nor suggests the making of nucleic acid constructs comprising calcineurin A and functional portions of calcineurin B, and thus the cited reference fails to anticipate the claimed invention.

The standard for anticipating a claim is clearly outlined in MPEP 2131, and this standard is further supported by the Courts. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1978). "The identical invention must be shown in as complete detail as is contained in the claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The cited reference fails to satisfy this standard. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

7. Claims 1, 3-4, 11, 20-21, 26, 28, 34, and 36 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Guerini et al., DNA, 1989, 8(9): 675-682 ("Guerini/DNA"). Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

The basis of this rejection is the same as that outlined in section 6 above. Clearly, as in section 6, the Examiner's interpretation of "portion" forms the basis of the rejection, and the rejection is moot when the term is interpreted in a manner consistent with the specification and with the structure of the claim in which it is used. Reconsideration and withdrawal of this rejection is respectfully requested.

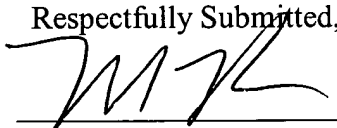
8. Claims 1, 5-11, 20, 23, 26, 28, 34, and 36 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Guerini/PNAS or Guerini/DNA in light of Chaudhuri et al. and Crabtree et al. Applicants traverse this rejection and contend that the rejection is moot in light of the amended claims.

As outlined in detail above, neither Guerini/PNAS nor Guerini/DNA satisfy the criteria for anticipating Applicants' invention, and Chaudhuri et al. and Crabtree et al. fail to overcome the deficiencies of Guerini/PNAS and Guerini/DNA. Reconsideration and withdrawal of this rejection are requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



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